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Initiation of antipsychotic treatment by general practitioners. A case–control study

Geartsje Boonstra MD MSc,[1]* Diederick E. Grobbee MD PhD,[2] Eelko Hak PhD,[3†] René S. Kahn MD PhD[4] and Huibert Burger MD PhD[5‡]

[1]Researcher, Intern Psychiatry, University Medical Centre Utrecht (UMCU), Rudolf Magnus Institute of Neuroscience (RMI), Department of Adult Psychiatry and Julius Centre for Health Sciences and Primary Care, Heidelberglaan, Utrecht, The Netherlands
[2]Professor of Clinical Epidemiology, UMCU, Julius Centre for Health Sciences and Primary Care, Heidelberglaan, Utrecht, The Netherlands
[3]Senior Researcher, UMCU, Julius Centre for Health Sciences and Primary Care, Heidelberglaan, Utrecht, The Netherlands
[4]Professor of Psychiatry, UMCU, RMI, Department of Adult Psychiatry, Heidelberglaan, Utrecht, The Netherlands
[5]Senior Researcher, UMCU, Julius Centre for Health Sciences and Primary Care, Heidelberglaan, Utrecht, The Netherlands

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Correspondence
Dr Geartsje Boonstra
University Medical Centre Utrecht
Location AZU
Division Hersenen
Department of Adult Psychiatry
HPN A00.241
Postbus 85500, 3508 GA, Utrecht
The Netherlands
E-mail: g.boonstra@umcutrecht.nl

*Address per September 1st 2009: RIAGG Amersfoort, Westsingel 46, 3811 BB Amersfoort, The Netherlands. Tel: +31-(0)33-4603500, Fax: +31-(0)33-4603599. E-mail: geartsje.boonstra@gmail.com.
†Current address: Department of Epidemiology, University Medical Center Groningen, Hanzeplein 1, Groningen, The Netherlands.
‡Current address: Department of Epidemiology and Department of Psychiatry, University Medical Center Groningen, Hanzeplein 1, Groningen, The Netherlands.

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Abstract

Rationale, aims and objectives Antipsychotics are approved treatment for severe conditions and have serious side effects. Antipsychotics are often prescribed off-label. Although a substantial proportion of antipsychotics are prescribed in primary care, it is largely unknown what motivates the general practitioner (GP) to *initiate* antipsychotic treatment. Therefore, we sought to examine the relation between pre-defined, licensed as well as off-label, reasons for antipsychotic treatment and the initiation of this treatment by the GP as well as report registration and incidence of antipsychotic treatment in general practice.
Methods In a case–control study, 723 patients selected from an electronic database and with a new antipsychotic prescription were compared with 3615 controls receiving any other new prescription. Using logistic regression, six pre-defined categories of International Classification of Primary Care (ICPC) codes ('psychosis', 'depression and anxiety', 'sleeping disorders', 'acute stress and surmenage', 'dementia' and 'somatic indications') were associated with initiating antipsychotic treatment.
Results All, including off-label, categories were significantly related to initiating antipsychotic treatment. The incidence of initiating antipsychotic therapy was 1.28 per 1000 persons per year (95% confidence interval: 1.09, 1.48). GPs registered an ICPC code in 50% and prescribed typical antipsychotics in 90% of the cases. Prescription of atypical antipsychotics increased almost threefold over the study period.
Conclusions The results suggest that GPs prescribe antipsychotics off-label. Despite serious side effects and relatively infrequent occurrence in Dutch general practices, GPs seem imprecise in underpinning and registrating the initiation of antipsychotic treatment. GPs increasingly prescribe atypical antipsychotics although the prescription of typical antipsychotics still dominates.

Introduction

Up to 80% of all antipsychotics are reported to be prescribed in primary care [1–5]. Furthermore, 1–3.2% of general practice patients receive antipsychotic drugs when investigated cross-sectionally and in approximately 10% of the general practitioner–patient encounters in which a psycho-active drug is prescribed an antipsychotic is among the prescribed drugs [2,4,6–8]. Thus, prescription of antipsychotics seems relatively common in general practice. Antipsychotics may induce serious side effects such as

tardive dyskinesia, Parkinsonism, akathisia, weight gain and sedation and enhance the risk of cerebrovascular incidents in some patient groups. Consequently, there has been concern about off-label use (Off-label use is defined as the use of a drug outside the licensed indication) of antipsychotics [1,6,9–12]. Although off-label use can partly be attributed to following guidelines based on proof from large randomized controlled trials, minimal evidence may support other off-label use. It is estimated that 30–50% of all prescriptions of antipsychotics are for off-label use [1,6,9,11]. However, it is largely unknown what conditions give rise to off-label antipsychotic prescribing by general practitioners (GPs). To investigate possible motives for off-label prescription, we associated six pre-defined diagnostic categories, four of them being off-label indications for antipsychotic treatment in the Netherlands, with new antipsychotic use in a case–control study using anonymous electronic medical records and pharmacy prescription data from a large population of GP patients in the Netherlands.

Methods

Database

Data were derived from the Almere Health Care Medical database, consisting of patients registered with approximately 110 GPs in 20 general practices in Almere in the Netherlands. Between 1999 and 2003, the population contributing to the database increased from 109 946 to 164 008 patients, thus representing a growing, large and dynamic population. GPs received training in systematic data entry and were financially compensated for providing data. Health problems and diagnoses were coded according to the International Classification of Primary Care (ICPC), version I with Dutch subtitles (2000) [13]. Linkage to pharmacy data from 17 pharmacies in the form of Anatomical Therapeutical Chemical Classification System-codes enabled the study of prescribing in relation to diagnosis.

Cases

Cases had to be registered in the database between 1 February 1999 and 31 December 2003 and be prescribed an antipsychotic by a GP, after a minimum of 12 months in which no antipsychotics were prescribed. By doing so, we selected cases of new antipsychotic prescribing which were then being arbitrarily defined.

Controls

Random selection of controls was done likewise. Only patients with whatever new medication prescription, except for antipsychotic prescriptions, were eligible. Like in cases, new medication prescribing was defined as the absence of a prescription of the same medication in the preceding 12 months. We aimed at selecting five controls per case to enhance precision of the association measure.

Exposure assessment

Prior to the analyses, health problems and diagnoses were selected that were hypothesized to be reasons for antipsychotic prescribing. This was done on content grounds while consulting two GPs. Subsequently, we clustered the selected ICPC codes in six diagnostic categories (see Table 1). ‘Depression and anxiety’, ‘sleeping disorders’, ‘acute stress and surmenage’ and ‘dementia’ are the four diagnostic categories that are off-label reasons for antipsychotic treatment. ‘Somatic indications’ is a diagnostic category consisting of three somatic symptoms that may or may not constitute an approved indication for antipsychotic therapy, depending on the symptoms’ severity and lack of earlier response to other than antipsychotic treatment. ‘Psychosis’ is the obvious on-label indication for the use of antipsychotics. This category was invoked to validate our data as it was expected to be highly associated with antipsychotic prescribing. Only ICPC codes recorded within an arbitrary time frame of –7 to +7 days around the prescription date were included. In case of two concurrent ICPC categories detected at one prescription occasion, the ICPC category diagnosed closest to the prescription date was selected.

Data analysis

Data were processed and analysed using SPSS 12.0 and Microsoft Excel SR-2. The yearly incidence of new antipsychotic prescribing was estimated as the number of cases in a particular year, divided by the number of persons in the database at the midpoint of that year. The incidence estimates per year were subsequently averaged over the total study period.

Logistic regression was used to calculate odds ratios (ORs) as measures of relative risk of the prescribing of antipsychotics for the diagnostic categories, while correcting for the potentially confounding variables age, gender and insurance status [14,15]. The reference category consisted of patients for which only ICPC codes other than the codes belonging to diagnostic categories under study were recorded or no ICPC code at all. The ORs were supplied with a 95% confidence interval (95% CI) as a measure of precision.

Results

A total of 2809 patients were identified as users of antipsychotics in the database. We excluded 1279 patients with less than 12 months of antipsychotic-free follow-up since 1 February 1999 and 789 patients because the new prescription was not performed by a GP. The remaining 723 cases were all included. Subsequently, 3615 controls were selected.

The incidence of initiating antipsychotic therapy was 1.28 per 1000 persons per year (95% CI: 1.09, 1.48). A frequency distribution of the different antipsychotic medications is shown in Fig. 1. It demonstrates that typical antipsychotics represent the vast majority of newly inititiated antipsychotic therapies (90.7%). The proportion of atypical antipsychotics increased over time from 4.7% in 2000 to 14.4% in 2003. Table 2 shows that the proportions of female gender and private insurance status are larger in controls than in cases. It further shows that mean age was substantially higher in the cases.

In 47.7% and 47.6% of cases and controls, respectively, no ICPC code was registered in the 14-day time interval (–7 days, +7 days) around the prescription date.

The logistic regression analysis showed substantially elevated probabilities of prescription for each diagnostic category compared with the reference category (Table 3). The ORs were all

Table 1 The six diagnostic categories of ICPC codes of interest

Diagnostic category	ICPC 2 codes	Full ICPC description
Psychosis	P20.4	Hallucinations/delusions
	P71.0	Other organic psychosis
	P71.1	Organic amnestic syndrome (excluding alcohol)
	P71.3	Other organic psychosis
	P72.0	Schizophrenia all forms
	P72.1	Schizophrenia
	P72.2	Delusional disorders
	P72.3	Non-organic psychoses
	P72.4	Schizo-affective disorders
	P72.5	Other schizophrenic disorders
	P73.0	Affective psychoses
	P73.1	Manic disorder
	P73.2	Bipolar disorder
	P98.0	Other not specified psychoses
	P98.2	Other not specified psychoses
	P99.0	Puerperal psychoses
Depression and anxiety	P01	Feeling anxious/nervous/tense
	P03	Feeling depressed
	P74	Anxiety disorder/anxiety state
	P76.0	Depressive disorder
	P76.1	Reactive depression
	P76.2	Other depressive disorder
Sleeping disorders	P06	Sleep disturbance
Acute stress and surmenage	P02.0	Acute stress reaction
	P02.1	Reaction to bereavement
	P02.2	Reaction to violence
	P02.3	Other acute stress reaction
	P78.0	Neuraesthenia/surmenage
	P78.1	Hyper aesthetic emotional syndrome
	P78.2	Other form of neuraesthenia/surmenage
Dementia	P70.0	Senile dementia/Alzheimer
	P70.1	Alzheimer's disease
	P70.2	Arteriosclerotic/multi-infarct dementia
	P70.3	Dementia as a consequence of another specific disorder
	P70.4	Other dementia
	P20.1	Orientation in time/place/person disturbed
	P20.2	Attention/concentration disorders
	P20.3	Amnesia all forms
Somatic indications	D09	Nausea
	D10	Vomiting
	R29.1	Hiccups

statistically significant, also after adjustment for the potential confounders. Changes in the ORs after adjustment were largely attributable to age. As expected, the OR for the validation category 'psychosis' was the highest. Excluding cases and controls in which no ICPC codes were registered resulted in slightly higher ORs for all categories (data not shown).

Discussion

Summary of main findings

Four ICPC diagnostic categories that have no approved indications for antipsychotic treatment in the Netherlands, that is, 'anxiety and depression', 'acute stress and surmenage', 'sleeping disorder' and 'dementia', were moderately to strongly associated with initiating antipsychotic therapy. In approximately half of the patients that were prescribed antipsychotics, no ICPC code was registered. The overall incidence of new antipsychotic prescribing was low, that is, 1.28 per 1000 person-years. Furthermore, GPs mainly prescribed typical antipsychotics; however, the incidence of initiating treatment with an atypical antipsychotic increased almost threefold over the study period.

Strengths and limitations

The high relative risk of prescription for the psychosis category supports the validity of our results. A further strength is that despite the relatively small numbers of patients in the diagnostic

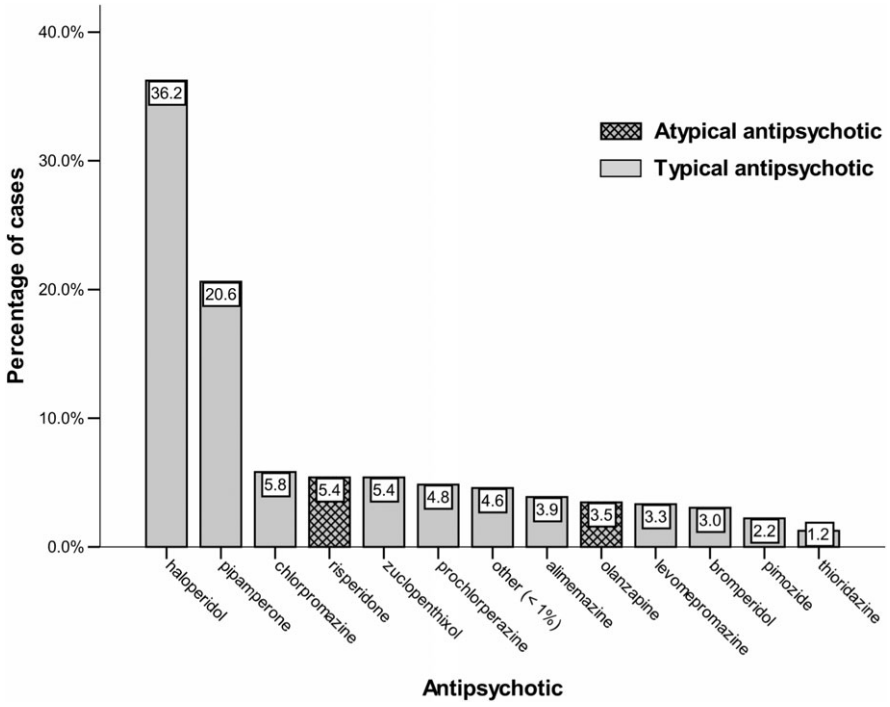

Figure 1 Bar chart showing the percentages of antipsychotics newly prescribed by the general practitioners in the cases. Different combinations ($n = 7$) of up to three different typical antipsychotics ($n = 10$), clozapine ($n = 2$), penfluridol ($n = 6$), periciazine ($n = 6$), perphenazine ($n = 1$), quetiapine ($n = 1$), sulpiride ($n = 6$), tetrabenazine ($n = 1$) and tiapride ($n = 1$) were combined to the category 'other (<1%)' as they were each prescribed in less then 1% of the cases.

Table 2 Characteristics of cases and controls

Variables	Controls ($n = 3615$)	Cases ($n = 723$)
Age, mean (range)	40.2 (1–101)	56.3 (0–101)
Gender		
Female, *n* (%)	2234 (61.8)	353 (48.8)
Insurance status, *n* (%)		
Private insurance	1068 (29.5)	151 (20.9)
State insurance	2547 (70.5)	572 (79.1)
Diagnostic categories, *n* (%)		
Psychosis	2 (0.1)	69 (9.5)
Depression and anxiety	46 (1.3)	30 (4.1)
Sleeping disorders	16 (0.4)	9 (1.2)
Acute stress and surmenage	15 (0.5)	7 (1.0)
Dementia	2 (0.1)	29 (4.0)
Somatic indications	16 (0.4)	40 (5.5)
Other ICPC codes diagnosed	1799 (49.8)	203 (28.1)
No ICPC code diagnosed	1719 (47.6)	345 (47.7)

Table 3 Crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for antipsychotic prescribing according to diagnostic category

Diagnostic categories	Crude OR (95% CI)	Adjusted* OR (95% CI)
Psychosis	225.2 (55.0, 921.2)	170.7 (41.3, 705.9)
Depression and anxiety	4.3 (2.7, 6.8)	4.5 (2.8, 7.4)
Sleeping disorders	3.7 (1.6, 8.4)	3.5 (1.4, 8.4)
Acute stress and surmenage	3.0 (1.2, 7.5)	3.6 (1.4, 9.1)
Dementia	94.6 (22.5, 397.8)	42.9 (9.7, 190.5)
Somatic indications	16.3 (9.1, 29.3)	17.5 (9.4, 32.6)

*Adjusted for age, gender and insurance status.

categories, the associations observed were fairly strong and all statistically significant.

The limitations of this study are largely inherent to the use of retrospectively collected health care data. The database did not provide information explicitly stating that the recorded ICPC codes were the reasons for prescribing antipsychotics, nor did it provide information about the past evolution and severity of the recorded problems, or about unregistered coexisting problems. Therefore, there could be other relevant reasons for GPs to prescribe antipsychotics explaining the association between the prescription and the analysed ICPC codes. However, we feel that the relations are likely to be largely real as in 84.6% of cases and controls where an ICPC code was registered, the day of registration coincided with the date of antipsychotic prescribing. Furthermore, a sensitivity analysis excluding all none-coinciding ICPC codes yielded higher risks for all categories in both adjusted and non-adjusted analyses.

The 12-month antipsychotics-free period prior to prescription, defining initiation of antipsychotic therapy, may have been too short. However, it seems unlikely that intermittent antipsychotic use was materially classified as new use because in only 4.8% of the cases a subsequent second antipsychotic-free period of at least 12 months was identified within the study period. Nonetheless, a source of bias may be that in 18 cases (2.5%) and in 253 controls (7.1%), the GP indicated it was a repeat prescription, even though there was a 12-month antipsychotic-free period preceding it. Because of the lack of clarity regarding the rules for registration of the indication 'repeat' by the GP, we ignored it in the selection of our cases and controls. A sensitivity analyses excluding these as 'repeat' marked prescription instances in cases and controls yielded similar ORs for all categories (data not shown).

Some of the approved indications for antipsychotics in the Netherlands, that is, agitation and restlessness and severe and treatment refractory anxiety, do not have separate ICPC codes in the Dutch ICPC registration systems. Obviously, the ICPC registration system is not designed specifically for registration of approved indications for antipsychotic treatment, but has to cover, mostly in more general terms, the entire spectrum of diagnoses and symptoms that can be encountered in the general practice. However, as the two mentioned approved indications for prescription of antipsychotics could coincide with any of the aforementioned four off-label diagnostic categories, especially 'dementia' and 'depression and anxiety', the relative risks for these categories may have been overestimated. Other reasons for recording one of the off-label categories could be reluctance to diagnose psychosis or incomplete skills or confidence for diagnosing and treating mental disorders [16,17].

In view of the above, it seems likely that our results reflect, at least partially, either off-label prescribing or incomplete registration or a combination of these factors.

A clear preference for prescribing typical antipsychotics, as opposed to atypical antipsychotics, was observed. This is in line with the guidelines of the Dutch College of General Practitioners (NHG) recommending typical antipsychotics as a first line of treatment [18].

Comparison with existing literature

The estimated incidence of the GP initiating antipsychotic treatment in the present study was 1.3 per 1000 person-years. Previously published studies reported higher rates of initiation of antipsychotic therapy by the GP, 3.3 and 10.1 per 1000 person-years, respectively [10,14,19]. When we included new antipsychotic prescriptions registered by any doctor, and not only by the GP, a higher incidence of 2.7 new prescriptions per 1000 person-years (95% CI: 2.40, 2.97) was found.

The population in Almere is relatively young in comparison with the general population in the Netherlands (source: Statistics Netherlands, Voorburg/Heerlen) while antipsychotics are more often prescribed to elderly people, as is reflected in the mean age shown in Table 2 [7]. When we projected our incidence rate to the age distribution of the general population in the Netherlands, the rate of new antipsychotic prescription by GPs was 1.69 per 1000 person-years (95% CI: 1.48, 1.91).

Our finding of considerable off-label prescribing of antipsychotics by GPs is consistent with previous work. A study by Mortimer showed that in the majority of cases, it was impossible to ascertain a diagnosis that suggested the need for antipsychotic treatment, despite professionals scrutinizing case notes and performing personal enquiries of the GPs [6]. A small retrospective Dutch study using questionnaires found that in 11% of the cases that used antipsychotics, in six general practices, the diagnosis was unknown [1]. The latter study also found that at least 76.9% of women and 40% of men were prescribed antipsychotics for approved indications, in case the GP made the diagnosis and initiated antipsychotic drug therapy, while in our study in 15.1% of all cases an on-label diagnosis was registered. In this study, the percentage increased to 28.8 if those cases were included where any ICPC code was registered and to 33.6 if additionally the date of registration and that of prescription coincided. One study performed in UK, including 200 randomly selected first-time users of antipsychotics of 10–99 years old, found that more than half of all incident antipsychotic use in the general practice was for non-approved indications such as depression, anxiety states and panic disorder, 15% for agitation and dementia, and less than 10% for the treatment of schizophrenia and other psychoses [19]. This study excluded less frequently prescribed antipsychotics. In agreement with our study, Trifiró *et al*. [10] reported that anxiety disorders were the most common off-label reason to prescribe typical antipsychotics in a general practice database.

The preference of the GP for prescribing typical antipsychotics in the present study (90% of the prescriptions) is consistent with the finding of Hamann *et al.*, who found 77% of typical antipsychotic first prescriptions, while, unlike the present study, prescription of low-potency antipsychotics and depot administrations were excluded from the analyses [3].

A UK study concerning the years 2000 and 2001 found that olanzapine and risperidone were the most frequently prescribed atypical medications, 45% and 38%, respectively (37.3% and 58.2% in our study, respectively) [20]. The proportion of initiated therapy with atypical antipsychotics by the GP increased almost threefold over the years 2000 (4.7%) to 2003 (14.4%) in the present study, consistent with incidence rates in Italy that increased similarly from 0.4 per 1000 person-years in 1999 to 1.3 per 1000 person-years in 2002 [10].

Implications for future research or clinical practice

Our results enforce the need for future prospective studies in general practice to prompt GPs to enter a diagnosis and an ICPC code at the moment of each prescription of antipsychotics, and simultaneously indicate any problem experienced in allocating proper ICPC codes to the patient. This will provide more robust data to confirm or disprove off-label prescribing of antipsychotics by the GP.

Conclusion

General practitioners do not often initiate antipsychotic therapy. In this study it seemed that, when initiating such treatment, the GP partially did this for off-label indications. Furthermore, at initiation of antipsychotic therapy there was no registration of an ICPC code in 50% of the cases, despite the rareness of the occasion and the severity of the approved indications for antipsychotic treatment. GPs preferred to prescribe typical rather than atypical antipsychotics, yet the proportion of initiated atypical antipsychotic therapy increased threefold from 2000 to 2004.

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